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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

June 20, 2002

Hon. Commissioner of Patents and Trademarks
Washington DC 20231

Applicant: Steven A. Benner
Title: A Method for Selecting Functional Deoxyribonucleotide Derivatives
Serial number: 09/415,966 Art Unit 1655
Filing date: October 12, 1999
Examiner. Lisa Arthur

Certificate of Mailing under 37 C.F.R. 1.8(a)

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Steven A. Benner (Applicant)

This is a verified statement that the Applicant is a "small entity" as defined by 37 CFR 1.27. The Applicant is a holder of Deposit Account Number 02-2055 in the Applicant' name,and authorizes the Commissioner to debit any charges or credit any overpayment to this account as appropriate.

This communication is responsive to an Office Action mailed March 21, 2002, Paper 11 in the above cited case.

COMMENTS ON THE RESTRICTION REQUIREMENT

The Applicant found the arguments made by the Examiner in favor of a restriction requirement compelling, at least to the extent that they appear to be an accurate application of the sections of the MPEP cited, in particular §806.05. The Applicant shall file separate continuations-in-part for the purpose of prosecuting the claims that were not "elected".

The status of Claim 31 is unclear, however. In Paper 11, Claims 3, 4, and 7-31 are stated to be pending. Claims 11-30 have been withdrawn from consideration because they are directed to a non-elected invention. Claim 9 is the subject of a 35 USC 112 (par 2) rejection. Claims 3, 4, 7, 8, and 9 are the subject of a 35 USC 112 (par 1) rejection.

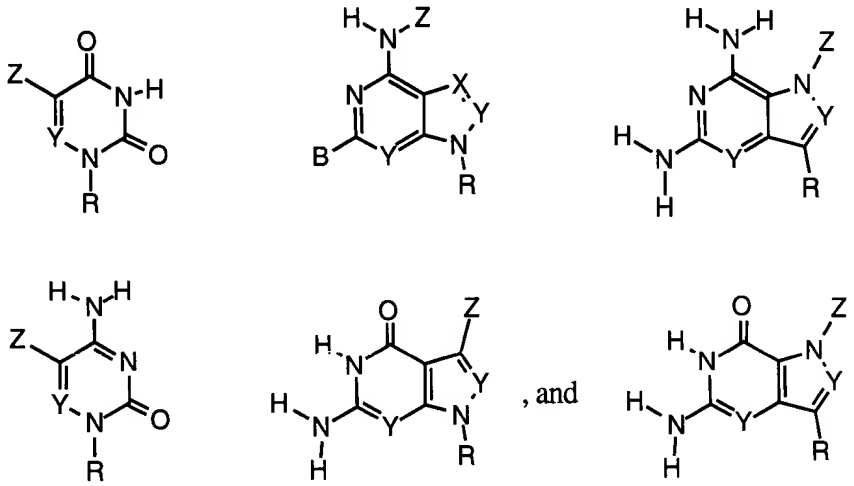
Claim 31, however, is neither the subject of a withdrawal from consideration based on a restriction requirement nor a rejection based on merits. Unless instructed otherwise, the Applicant assumes that Claim 31 is allowed.

AMENDMENTS TO THE CLAIMS

Please make the following amendments to the claims specified below:

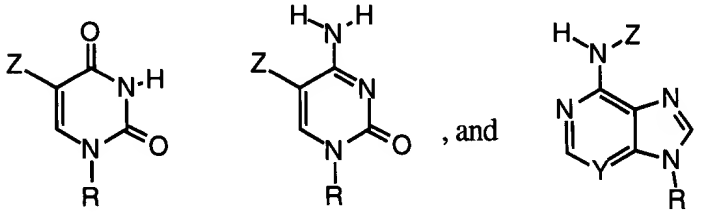
Claim 3 (amended). An [The] improvement [of claim 1 wherein said nucleobase is] in a method for creating a ligand for a target compound, said method comprising:
a) synthesizing a mixture of oligonucleotides from nucleotide building blocks each of the oligonucleotides having a region of randomized sequence,
b) contacting said mixture with the target, wherein oligonucleotides having an increased affinity to the target relative to others in the mixture may be partitioned from the remainder of the mixture,

c) partitioning the oligonucleotides with increased affinity from the other oligonucleotides in the mixture,
d) amplifying the oligonucleotides having increased affinity *in vitro* to yield a mixture of oligonucleotides enriched in those with increased affinity for said target,
wherein the improvement comprises including among said nucleotide building blocks those carrying nucleobases selected from the group consisting of



wherein -R designates the point of attachment to the ribose or 2'-deoxyribose ring, B is selected from the group consisting of -H or $-NH_2$, X is either a nitrogen atom or a carbon atom bearing a substituent Z, Z is [either a hydrogen,] an unfunctionalized lower alkyl, alkynyl, or alkyl-alkynyl chain, or a lower alkyl, alkynyl , or alkyl-alkynyl chain bearing an amino, carboxyl, hydroxy, thiol, aryl, indole, or imidazoyl group, Y is either N or CH, and the ring contains no more than three nitrogens consecutively bonded.

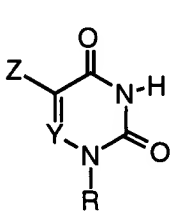
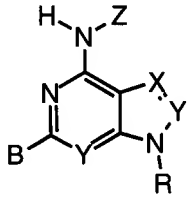
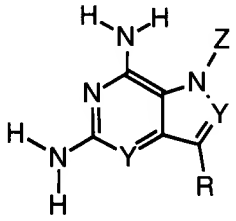
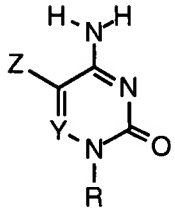
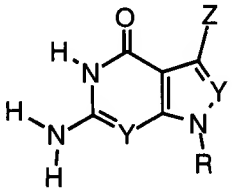
Claim 4 (amended). The improvement of Claim [1] 3 wherein said nucleobase is selected from the group consisting of



wherein -R designates the point of attachment to the ribose or 2'-deoxyribose ring, and wherein Z is selected from the group consisting of $-C\equiv C-CH_2-NH_2$, $-C\equiv C-CH_2-SH$, $-CH_2CH_2CH_2-NH_2$, $-CH_2CH_2CH_2-SH$, $-CH_2-NH_2$, $-CH_2-SH-$, $CH_2CH_2-NH_2$, $-CH_2CH_2-SH$, $-CH_2CH_2CH_2$-imidazole, $-CH_2CH_2$-imidazole, lower alkyl, $-CH_2$-imidazole, and $-CH_2CH_2CH_2CH_2CH_2CH_2-NH_2$.

Claim 7 (amended). An [The] improvement [of claim 6 wherein said nucleobase is] in a method for creating a catalyst for a preselected reaction, said method comprising:
a) synthesizing a mixture of oligonucleotides from nucleotide building blocks each having a region of randomized sequence
b) incubating said mixture under conditions where oligonucleotides that catalyze said reaction undergo as a result of their catalytic activity a chemical transformation that makes them preferentially [partitionable] separable from other oligonucleotides in the mixture having less catalytic activity [or amplifiable to oligonucleotides in the remainder of the mixture that have diminished or none of said catalytic activity],

c) [partitioning] separating the oligonucleotides with increased catalytic activity from the other oligonucleotides in the mixture
d) [amplifying] copying the oligonucleotides having increased [affinity] catalytic activity *in vitro* to yield a mixture of oligonucleotides enriched in those with increased [affinity] catalytic activity [for said target],
wherein the improvement comprises including among said nucleotide building blocks those carrying nucleobases selected from the group consisting of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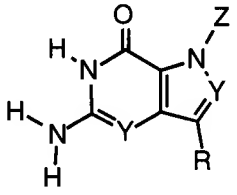
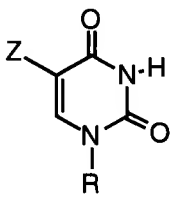
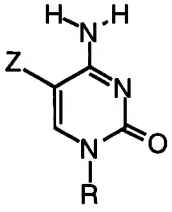


wherein -R designates the point of attachment to the ribose or 2'-deoxyribose ring, B is selected from the group consisting of -H or -NH_2, X is either a nitrogen atom or a carbon atom bearing a substituent Z, Z is [either a hydrogen,] an unfunctionalized lower alkyl, alkynyl, or alkyl-alkynyl chain, or a lower alkyl, alkynyl , or alkyl-alkynyl chain bearing an amino, carboxyl, hydroxy, thiol, aryl, indole, or imidazoyl group, Y is either N or CH, and the ring contains no more than three nitrogens consecutively bonded.

Claim 8 (amended). The improvement of Claim [6] 7, wherein said nucleobase is selected from the group consisting of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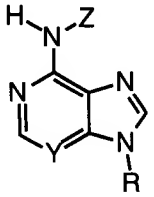

wherein -R designates the point of attachment to the ribose or 2'-deoxyribose ring, and wherein Z is selected from the group consisting of -C≡C-CH_2-NH_2, -C≡C-CH_2-SH, -$CH_2CH_2CH_2$-NH_2, -$CH_2CH_2CH_2$-SH, -CH_2-NH_2, -CH_2-SH-, CH_2CH_2-NH_2, -CH_2CH_2-SH, -$CH_2CH_2CH_2$-imidazole, -CH_2CH_2-imidazole, lower alkyl, -CH_2-imidazole, and -$CH_2CH_2CH_2CH_2CH_2CH_2$-NH_2.]

Claim 9 (amended). An improvement in a method for creating a catalyst for a preselected reaction, said method comprising:
a) synthesizing a mixture of oligonucleotides from nucleotide building blocks each having a region of randomized sequence
b) incubating said mixture under conditions where oligonucleotides that catalyze said reaction undergo as a result of their catalytic activity a chemical transformation that makes them preferentially [partitionable] separable from other oligonucleotides in the mixture having less catalytic activity [or amplifiable to oligonucleotides in the remainder of the mixture that have diminished or none of said catalytic activity],

c) [partitioning] separating the oligonucleotides with increased catalytic activity from the other oligonucleotides in the mixture
d) [amplifying] copying the oligonucleotides having increased [affinity] catalytic activity *in vitro* to yield a mixture of oligonucleotides enriched in those with increased [affinity] catalytic activity [for said target],
wherein said improvement comprises:
e) including an organic cofactor during step (b) [an organic cofactor], wherein said organic cofactor [carries an organic functional group that] binds noncovalently to the oligonucleotides [so enriched] and carries functionality not present on natural oligonucleotides.

COMMENTS ON THE AMENDMENTS TO THE CLAIMS

Claims 3, 4, 7, and 8 were objected to because they depended on a cancelled claim. The amendments in each case follow the suggestion of the Examiner to include within their text the body of the cancelled claim upon which they were dependent.

Claim 9 is rejected as being indefinite, broad, and unclear. The amendment first replaces the recitation "amplifiable to oligonucleotides" by a passage that makes clear what chemical transformation is occurring. The amendment then replaces the phrase "oligonucleotides so enriched" with a phrase that has clear antecedent basis. Last, the amendment attempts to address the issues of breadth and clarity raised in the 35 USC 112 (par 1) rejection.

TRAVERSAL OF THE REJECTIONS

A 35 USC 112 (par. 1) rejection was based on the assertion that the specification "does not provide sufficient guidance to enable the skilled artisan to make and use the claimed invention without undue experimentation "because of the unpredictability of a polymerase to incorporate a non-natural nucleotide into a polynucleotide". Without addressing the very broad question of whether a polymerase can incorporate *any* nucleotide analog, the instant invention is drawn to a very specific class of nucleotide analogs, those bearing substituents on the 5-position of the pyrimidine (or pyrimidine analog) ring, or on the 6 or 7-positions of a standard or 7-deazapurine (or the analogous position of a purine analog) (see specification page 8, lines 5-8; and Examples 1 and 2, which describes the preparation of 5-position modified uridine and 2'-deoxyuridine analogs, and Example 3, which describes the preparation of 6-position modified adenosines).

The Examiner seems to understand this, if we correct one minor error. The Applicant respectfully believes that the Examiner has erred on page 5 (second line from bottom) in suggesting that the specification states that Klenow fragment can incorporate many pyrimidines (derivatized?) at the 5'-position. The 5'-position is on the ribose ring; as this position participates in the joining of a phosphodiester bond, it is difficult for modification at the 5'-position to be incorporated into a DNA chain, by a polymerase or by non-polymerase methods. Rather, the specification teaches modification at the 5 position (on the pyrimidine ring), as the Examiner states in the previous line.

The Examiner then suggests that "the instant specification contains no teaching that the modified uridine nucleotides pair with a specific modified or natural purine. The specification does not actually demonstrate that the claimed nucleotides can be incorporated into a polynucleotide by a polymerase or that oligonucleotides containing these modifications can function as templates in an amplification reaction. The ability of a non-natural nucleotide to be used by polymerases in general or a specific polymerase was highly unpredictable and unexpected at the time of the filing".

The Applicant respectfully traverses the comments made in each of these three sentences, with respect to 5-position derivatized uridines, and 6 or 7-position derivatized purines. Before the parent application was filed in 1990, several laboratories had reported that polymerases incorporated 5-position modified uridines, and this work was incorporated by reference in the specification. The Examiner's attention is respectfully drawn to page 9 (lines 5-9), where work done (and patented) by David Ward in 1981. These carried biotin on an alkenyl linker attached to the 5-position of 2'-deoxyuridine. Likewise, work by Prober et al. (Prober, JM, Trainor GL,

The Examiner also questions the enablement of the portion of the invention that considers cofactors. This question is distinct from enablement issues related to the question whether polymerases incorporate 5-position derivatized pyrimidines and 6- or 7-position derivatized pyrimidines.

Here, the Examiner's objections are less clear. Page 6 (lines 13-15) imply that the breadth of Claim 9 is problematic. The following line suggests that the clarity of the claim is at issue. Some of the Examiner's confusion is undoubtedly due to poor drafting of Claim 9. An effort has been made to re-draft Claim 9 to make it narrower and clearer.

The applicant is, however, able to traverse some specific objections to Claim 9 raised by the Examiner. Thus, the Examiner finds it unclear how the cofactor "selectively associates with only the catalytic oligonucleotides." This suggests a misunderstanding of the invention. According to the instant invention, it is the association of the cofactor with the oligonucleotide that catalytic power is conferred on the oligonucleotide conjugate. The cofactor has no special ability to associate with oligonucleotides that are catalytic in their own right, that is, without having bound a cofactor.

"The skilled artisan would ... be required to perform additional extensive experimentation without a reasonable expectation of ... whether the cofactors could be used in a method for identifying catalytic oligonucleotides." This, respectfully, is a misunderstanding of the instant invention. The instant invention is an improvement on previously patented inventions that cover a process that generates catalytic oligonucleotides by making a mixture of random oligonucleotides and then applying selection steps to this mixture, whereby oligonucleotides that have catalytic activity survive the selection. The improvement is to add cofactors carrying functionality to increase the likelihood that good catalysts will emerge from this process. The cofactors are not, in this improved process, used "for identifying catalytic oligonucleotides." Again, we hope that the amendment of Claim 9 will help the reader understand this.

Likewise, the Examiner finds it unclear how a cofactor "is to effect catalytic activity or to result in catalytic activity if the cofactor is to have any effect at all on catalytic activity". The specification discusses at length (see discussion starting on page 7, line 4 ff) why one of ordinary skill in the art expects adding cofactors to a library will enhance catalytic activity. This is the case even for proteins (page 7, line 10), where cofactors carry aldehyde or ketone functionality (line 11), redox activity (line 12), and so on. But it should be noted that it is an inherent feature of the *in vitro* selection process (covered by previous patents by Gold, for example), as well as the improved process (the instant invention), that one need not have an explicit understanding of exactly how a cofactor confers catalytic activity for one to find an improved process that uses cofactors to be useful.

Respectfully submitted,

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